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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/663,857	09/15/2003	Yeon-su Lee	YPL-0064	4107

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EXAMINER	
BERTAGNA, ANGELA MARIE	

ART UNIT	PAPER NUMBER
1637	

DATE MAILED: 11/27/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/663,857	LEE ET AL.	
	Examiner	Art Unit	
	Angela Bertagna	1637	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *18 October 2006*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-6* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-6* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *8/28/06*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

FINAL REJECTION

Status of the Application

1. Applicant's response filed October 18, 2006 is acknowledged. Claims 1-6 are currently pending. Claim 1 was amended in the response.

Claim Rejections - 35 USC § 112

2. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-6 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

Factors to be considered in determining whether a disclosure meets the enablement requirement of 35 USC 112, first paragraph, have been described by the court in *In re Wands*, 8 USPQ2d 1400 (CA FC 1988). *Wands* states at page 1404,

> "Factors to be considered in determining whether a disclosure would require undue experimentation have been summarized by the board in Ex parte Forman. They include (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims."

Enablement issues

There are two fundamental enablement issues in the instant claims. First, the claims recite that two variant polynucleotides function individually to: (a) diagnose maturity onset diabetes of the young (MODY) or (b) predict an individual's risk of developing MODY. Secondly, there is significant variability and unpredictability as to whether the claimed single nucleotide polymorphisms (SNPs) actually function to diagnose MODY or predict a patient's risk of developing the disease.

The nature of the invention

Claim 1 is drawn to a nucleic acid fragment for the diagnosis of maturity onset diabetes of the young (MODY) or the risk of MODY in humans. The fragment comprises 10 or more contiguous nucleotides from SEQ ID NO: 1 or SEQ ID NO: 3. In addition, the fragment includes a G->A substitution at position 1699 in SEQ ID NO: 1 or a C->T substitution at position 29 in SEQ ID NO: 3. The invention is in a class of invention that the CAFC has characterized as "the unpredictable arts such as chemistry and biology." Mycogen Plant Sci., Inc. v. Monsanto Co., 243 F.3d 1316, 1330 (Fed. Cir. 2001).

The breadth of the claims

Claim 1 is drawn to an isolated nucleic acid containing a particular single nucleotide polymorphism (SNP) that functions as a predictive diagnostic marker for MODY.

Quantity of Experimentation

The quantity of experimentation in this area is immense, since there is complete variability as to whether or not the observation of a particular SNP in a given patient is capable of functioning as a predictor of disease susceptibility. It would require significant study and experimentation including trials with hundreds of patients from multiple ethnic populations to determine that a single SNP is capable of reliably predicting the susceptibility of any patient to MODY. This would be an inventive, unpredictable and difficult undertaking in itself, and the efficacy of the SNP as a susceptibility predictor for any particular disease would need to be demonstrated in a variety of patients with a statistically significant result. This would require years of inventive effort, with each of the many intervening steps, upon effective reduction to practice, not providing any guarantee of success in the succeeding steps.

Wacholder et al. (J. Natl. Cancer Institute (2004) 96(6): 434-442) notes that in studies of the association of mutations with specific diseases larger studies with 1500 participants have significantly more statistical power than smaller studies (see page 435). In other words, the quantity of experimentation factor supports the conclusion that a large quantity of experimentation, with the use of many hundreds, perhaps even thousands, of patient samples would be necessary to demonstrate an association between the claimed SNP and a specific neurological disorder. In order to cover any fraction of the possible neurological disorders in even one population, hundreds of thousands of separate patients and the associated analyses would be required. This is a very large amount of experimentation.

The prior art of Lee et al. (Acta Diabetologica (2001) 38: 123-127) and Rissanen et al. (Diabetes Care (2000) 23(10): 1533-1538; cited on IDS) illustrates the quantity of

experimentation necessary to determine an association between a given polymorphic variant and MODY. Lee sought to determine whether or not mutations in the HNF-1a gene were associated with MODY in a Korean population (see abstract). Lee analyzed genomic DNA from 69 unrelated subjects diagnosed with MODY and 35 healthy controls by PCR and SSCP (page 124) and identified five polymorphisms (see abstract and Table 2). One polymorphism was a silent mutation. The frequencies of the other four polymorphisms were not found to differ significantly from the control population (see abstract and Table 2). Despite this, one polymorphism (S487N) was tested further. However, no relationship between the polymorphism and clinical diagnostic factors was identified (see abstract and Table 3). Similarly, Rissanen teaches that although an A98V substitution in the HNF-1a gene was observed more frequently in Finnish diabetic patients compared to control subjects, this mutation was not associated with clinical factors in MODY (see results section on page 1533). These results of Lee and Rissanen provide specific examples of observed polymorphisms that did not ultimately display predictive or diagnostic capabilities, thereby leading to a loss of time and experimental resources without positive gain.

Unpredictability in the Art and State of the Prior Art

The prior art teaches that mutations in the HNF-1a gene are often observed in MODY patients, but does not teach or suggest analysis of the claimed polymorphic variant. Also, although the prior art identifies HNF-1a mutations in MODY patients, it does not teach diagnosis or susceptibility prediction based solely on the presence of a single SNP. For example, Vaxillaire et al. (Human Molecular Genetics (1997) 6(4): 583-586; cited on IDS) identified 10

mutations in the HNF-1a gene of MODY patients (see abstract and Table 1), but did not identify either of the claimed SNPs or use the identified SNPs to diagnose or predict susceptibility to MODY. Similarly, Hansen et al. (Diabetes (1997) 46: 726-730; cited on IDS) identified five mutations in the HNF-1a gene of MODY patients (see abstract and Figure 1), but did not identify either of the claimed SNPs or use the identified SNPs to diagnose or predict susceptibility to MODY.

The art also teaches that it is entirely unpredictable whether or not mutations in the HNF-1a gene are associated with MODY. For example, Johansen et al. (The Journal of Clinical Endocrinology and Metabolism (2005) 90(8): 4607-4614) screened the HNF-4a, GCK, and HNF-1a (synonymous with TCF1) genes of MODY patients (38 families, 351 individuals) for mutations (see abstract). These authors identified mutations in the three examined genes in only 49% of the patients studied (see abstract). Johansen further stated, "In the majority of Danish Caucasion MODY probands, we found no mutations in TCF1, GCK, or HNF4A....It is possible that MODY in Denmark to a greater extent is caused by mutations in genes other than TCF1, GCK, or HNF4A (page 4612, column 2)." Similarly, Bjorkhaug et al. (The Journal of Clinical Endocrinology and Metabolism (2003) 88(2): 920-931) screened 130 Norwegian families for HNF-1a mutations (see abstract). Bjorkhaug identified mutations in 52% of patients with clinical MODY, but only 20% of patients with suspected MODY (page 930, column 2). These results of Johansen and Bjorkhaug suggest that for an undiagnosed patient, it is entirely unpredictable whether or not a given SNP is capable of predicting or diagnosing MODY in the absence of additional testing.

Finally, the art is replete with evidence that gene association studies are typically wrong. In fact, Lucentini et al (The Scientist (2004) Vol 18) titled his article "Gene Association Studies Typically Wrong" and states "Two recent studies found that typically, when a finding is first published linking a given gene with a complex disease, there is only roughly a one-third chance that studies will reliably confirm the finding (see page 2 of the reference)." This is consistent with the teaching of Wacholder et al (J. Natl. Cancer Institute (2004) 96(6): 434-442) who notes, "Too many reports of associations between genetic variants and common cancer sites and other complex diseases are false positives" (see abstract). Ioannidis (Nature genetics (2001) 29:306-309) further supports this conclusion in pointing out the heterogeneity of results among different studies of genetic polymorphisms (see abstract, for example).

Therefore, the art suggests that it is unclear whether the claimed SNPs reliably function as a diagnostic or susceptibility index in MODY, and further suggests that many reported associations between SNPs and a particular disease may be incorrect, thereby providing support for the conclusion that it is entirely unpredictable whether a given polymorphic variant will function in a diagnostic or predictive capacity for a given disease in a particular population. In short, the teachings of Lee, Rissanen, Bjorkhaug, and Johansen highlight the unpredictability inherent in the art and the enormous quantity of experimentation required to determine that a given SNP functions as a diagnostic or susceptibility marker for MODY, and additionally emphasizes the fact that different subject populations require the same extensive experimentation to determine the predictive properties of the same SNP and that functional data should support an observed genetic correlation.

Working Examples

The specification provides four working examples. Example 1 describes amplification of HNF-1a exon 10 DNA from 97 patients clinically presumed as MODY patients (i.e. patients with known disease status) (pages 5-7). Example 2 describes sequencing of the amplified DNA (page 7). Example 3 describes detecting SNPs in the sequencing results (page 7). Example 3 further teaches that mutations in exon 10 were found in only 4 of the 97 patients tested, and a new mutation (the claimed G->A substitution at position 1699) was found in only one of these four patients (page 7). Example 4 describes repetition of the process to analyze the MODY3 intron, and further teaches that the claimed C->T substitution at position 29, was found in only one of the 97 patients tested. The working examples do not present any data (for example, in the form of data tables or gel photographs) to support the text. The results of the study also were not replicated and studies in different ethnic populations were not conducted.

Guidance in the Specification

The specification asserts that the claimed SNPs are useful for diagnosing or predicting any patient's susceptibility to MODY (see pages 4-5, for example). However, the specification only presents a single observance (non-replicated) of the claimed SNPs in a single patient of known disease status taken from a small study population. Since the working examples were conducted using samples from patients with known MODY status, they function as a means of assay validation rather than a means of diagnosing subjects with unknown disease status or predicting a subject's risk of developing MODY. Finally, the specification provides no guidance on methods or techniques to demonstrate an association between MODY and the claimed SNPs.

The specification even fails to provide any discussion or description of the scientific steps necessary to provide evidence that would associate a particular SNP with MODY. Therefore, in order to determine the functional limitation of the claimed SNPs appearing in the preamble, an ordinary practitioner would be required to screen an enormous number of patients from different populations and then determine if a correlation exists between the presence of the claimed SNPs and susceptibility to the particular condition in the specific study population using the vast quantity of experimentation replete with the potential for negative results discussed above.

Level of Skill in the Art

The level of skill in the art is deemed to be high.

Conclusion

In the instant case, as discussed above, the level of unpredictability in the ability of the claimed SNPs to diagnose or predict the susceptibility of subjects to MODY, where only a single specific example has been provided in the specification, combined with the negative teachings in the art regarding the association of HNF-1a polymorphisms with MODY and the negative teachings of Wacholder, Ioannidis, and Lucentini regarding association studies in general, supports a finding of undue experimentation. The specification provides no written description or guidance that leads one to a reliable method of associating the claimed polymorphism with MODY diagnosis or MODY susceptibility. Furthermore, the specification does not provide guidance to overcome art-recognized problems in the association of single nucleotide polymorphisms with susceptibility to specific diseases or conditions (see Wacholder, Ioannidis,

and Lucentini, discussed above). Finally, the quantity of experimentation is immense. Thus, given the broad claims in an art whose nature is identified as unpredictable, the unpredictability of that art, the large quantity of research required to define these unpredictable variables, the lack of guidance provided in the specification, the limitations of the working examples and the negative teachings in the prior art balanced only against the high skill level in the art, the inevitable conclusion is that it would require undue experimentation for one of skill in the art to determine the functional limitation of the claim as broadly written.

Claim Rejections - 35 USC § 102

3. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.
>
> (e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

4. Claims 1-4 are rejected under 35 U.S.C. 102(b) as being anticipated by Emens et al. (PNAS (1992) 89(16): 7300-7304).

Regarding claim 1, Emens teaches a nucleic acid fragment comprising a polymorphic site of SEQ ID No: 1 having adenine at position 1699 and comprising more than 10 contiguous nucleotides of SEQ ID No: 1 (see alignment below, where the corresponding fragment is underlined). This alignment was generated from GenBank Accession No. M95297, deposited by Emens et al. (see attached GenBank printout), and cited in the PNAS reference (page 7300).

```
RESULT 15
HAMHNF1A
LOCUS       HAMHNF1A                2452 bp    mRNA    linear   ROD 27-APR-
1993
DEFINITION  Mesocricetus auratus (clone 2.5) hepatocyte nuclear factor 1-alpha
            (HNF1a) mRNA sequence.
ACCESSION   M95297
VERSION     M95297.1  GI:191386
KEYWORDS    hepatocyte nuclear factor 1-alpha.
SOURCE      Mesocricetus auratus (golden hamster)
  ORGANISM  Mesocricetus auratus
            Eukaryota; Metazoa; Chordata; Craniata; Vertebrata; Euteleostomi;
            Mammalia; Eutheria; Euarchontoglires; Glires; Rodentia;
            Sciurognathi; Muroidea; Cricetidae; Cricetinae; Mesocricetus.
REFERENCE   1  (bases 1 to 2452)
  AUTHORS   Emens,L.A., Landers,D.W. and Moss,L.G.
  TITLE     Hepatocyte nuclear factor 1 alpha is expressed in a hamster
            insulinoma line and transactivates the rat insulin I gene
  JOURNAL   Proc. Natl. Acad. Sci. U.S.A. 89 (16), 7300-7304 (1992)
   PUBMED   1380153
COMMENT     Original source text: Mesocricetus auratus (library: HIT) pancreas
            cDNA to mRNA.
FEATURES             Location/Qualifiers
     source          1. .2452
                     /organism="Mesocricetus auratus"
                     /mol_type="mRNA"
                     /db_xref="taxon:10036"
                     /cell_line="T15 M.2.2.2"
                     /cell_type="islet"
                     /tissue_type="pancreas"
                     /tissue_lib="HIT"
ORIGIN

  Query Match             81.6%;  Score 1547.2;  DB 6;  Length 2452;
  Best Local Similarity   88.9%;  Pred. No. 0;
  Matches 1685;  Conservative    0;  Mismatches  208;  Indels    3;  Gaps
1;

Qy          1 ATGGTTTCTAAACTGAGCCAGCTGCAGACGGAGCTCCTGGCGGCCCTGCTCGAGTCAGGG 60
              ||||||||||||||| |||||||||||||||||||||||| |||||||||||||| ||
Db         84 ATGGTTTCTAAACTCAGCCAGCTGCAGACGGAGCTCCTGGCTGCCCTGCTCGAGTCCGGC 143

Qy         61 CTGAGCAAAGAGGCACTGATCCAGGCACTGGGTGAGCCGGGGCCCTACCTCCTGGCTGGA 120
              ||||| || |||||  |||| |||||  |||| ||||| ||||||||||  ||| ||||
Db        144 CTGAGTAAGGAGGCTTTGATTCAGGCCTTGGGGGAGCCAGGGCCCTACCTGATGGTTGGA 203

Qy        121 GAAGGCCCCCTGGACAAGGGGGAGTCCTGCGGCGGCGGTCGAGGGGAGCTGGCTGAGCTG 180
              || |  |||||||||||||||||||||||| | ||  ||||||| || ||||| ||||||
Db        204 GATGCTCCCCTGGACAAGGGGGAGTCCTGCAGTGGGAGTCGAGGTGACCTGGCCGAGCTG 263

Qy        181 CCCAATGGGCTGGGGGAGACTCGGGGCTCCGAGGACGAGACGGACGACGATGGGGAAGAC 240
              |||||||| ||||||||| | || | ||| || ||||| ||||| || ||||||||||||
Db        264 CCCAATGGCCTGGGGGAGTCGCGTGTCTCGGAAGACGACACGGATGATGATGGGGAAGAC 323
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Qy       241 TTCACGCCACCCATCCTCAAAGAGCTGGAGAACCTCAGCCCTGAGGAGGCGGCCCACCAG 300
             ||| |||||||||| || |||||| ||||||||||||||| |||||||| |||||||||
Db       324 TTCGCGCCACCCATTCTGAAAGAGTTGGAGAACCTCAGCCCGGAGGAGGCAGCCCACCAG 383

Qy       301 AAAGCCGTGGTGGAGACCCTTCTGCAGGAGGACCCGTGGCGTGTGGCGAAGATGGTCAAG 360
             |||||||||||||||| | |||||||||| |||||||||||||||| ||||||||||||
Db       384 AAAGCCGTGGTGGAGTCGCTTCTGCAGGACGACCCGTGGCGTGTGGCAAAGATGGTCAAG 443

Qy       361 TCCTACCTGCAGCAGCACAACATCCCACAGCGGGAGGTGGTCGATACCACTGGCCTCAAC 420
             |||||  ||||||||||||| ||||| |||||||||||||||||| ||||| || ||||||
Db       444 TCCTATTTGCAGCAGCACAATATCCCGCAGCGGGAGGTGGTCGACACCACGGGTCTCAAC 503

Qy       421 CAGTCCCACCTGTCCCAACACCTCAACAAGGGCACTCCCATGAAGACGCAGAAGCGGGCC 480
             |||||||||||||| || |||||||||||||||| |||||||||||||||||||||||||
Db       504 CAGTCCCACCTGTCGCAGCACCTCAACAAGGGCACGCCCATGAAGACGCAGAAGCGGGCC 563

Qy       481 GCCCTGTACACCTGGTACGTCCGCAAGCAGCGAGAGGTGGCGCAGCAGTTCACCCATGCA 540
             || ||||||||||||||||||||||||||||||||||||| ||||| |||||||| ||
Db       564 GCTCTGTACACCTGGTACGTCCGCAAGCAGCGAGAGGTGGCTCAGCAATTCACCCACGCG 623

Qy       541 GGGCAGGGAGGGCTGATTGAAGAGCCCACAGGTGATGAGCTACCAACCAAGAAGGGGCGG 600
             ||||| || || ||||| |||||||||| ||||| ||||| || ||||| |||||  ||
Db       624 GGGCAAGGGGGACTGATCGAAGAGCCCACCGGTGACGAGCTGCCGACCAAAAAGGGAAGG 683

Qy       601 AGGAACCGTTTCAAGTGGGGCCCAGCATCCCAGCAGATCCTGTTCCAGGCCTATGAGAGG 660
             |||||||| |||||||||||||| ||||||||||||||||||||||||||||||||||||
Db       684 AGGAACCGGTTCAAGTGGGGCCCGGCATCCCAGCAGATCCTGTTCCAGGCCTATGAGAGG 743

Qy       661 CAGAAGAACCCTAGCAAGGAGGAGCGAGAGACGCTAGTGGAGGAGTGCAATAGGGCGGAA 720
             |||||||| || |||||||| ||||| |||||  | |||||||||| || ||||||||
Db       744 CAGAAGAATCCCAGCAAGGAAGAGCGGGAGACCTTGGTGGAGGAGTGTAACAGGGCGGAG 803

Qy       721 TGCATCCAGAGAGGGGTGTCCCCATCACAGGCACAGGGGCTGGGCTCCAACCTCGTCACG 780
             |||||||||||| |||||||| |||||||||||||||||| |||||||||| ||||||
Db       804 TGCATCCAGAGGGGGGTGTCACCATCACAGGCACAGGGGCTAGGCTCCAACCTTGTCACG 863

Qy       781 GAGGTGCGTGTCTACAACTGGTTTGCCAACCGGCGCAAAGAAGAAGCCTTCCGGCACAAG 840
             |||||||||||||||||||||||||||||||||||||||| |||||||||| |||||||||
Db       864 GAGGTGCGTGTCTACAACTGGTTTGCCAACCGGCGCAAGGAAGAAGCCTTTCGGCACAAG 923

Qy       841 CTGGCCATGGACACGTACAGCGGGCCCCCCCCAGGGCCAGGCCCGGGACCTGCGCTGCCC 900
             |||||||||||||| |||| ||| ||||| ||  |||||||||| ||  |  | ||| |
Db       924 CTGGCCATGGACACATACAACGGACCCCCACCCAGGCCAGGCCCAGGCGCCACACTGTCT 983

Qy       901 GCTCACAGCTCCCCTGGCCTGCCTCCACCTGCCCTCTCCCCCAGTAAGGTCCACGGTGTG 960
             |||||||||||||||||||||||  || | ||||||||||||||||||||||||||||||
Db       984 GCTCACAGCTCCCCTGGCCTGCCCACATCCGCCCTCTCCCCCAGTAAGGTCCACGGTGTG

Qy       961 CGCTATGGACAGCCTGCGACCAGTGAGACTGCAGAAGTACCCTCAAGCAGCGGCGGTCCC
             || || |||||||||| ||||||||| | || || || |||||||||||||| ||||||
Db      1044 CGGTACGGACAGCCTGCAACCAGTGAGGCAGCTGAGGTGCCCTCAAGCAGCGGTGGTCCC

Qy      1021 TTAGTGACAGTGTCTACACCCCTCCACCAAGTGTCCCCCACGGGCCTGGAGCCCAGCCAC
             |||||||||||||||  |  |  | |||||||||| ||||| ||||||||||||||  |
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Db       1104 TTAGTGACAGTGTCTGCGGCTTTACACCAAGTGTCGCCCACAGGCCTGGAGCCCAGCAGC

Qy       1081 AGCCTGCTGAGTACAGAAGCCAAGCTGGTCTCAGCAGCTGGGGGCCCCCTCCCCCCTGTC
             |||||||||||  ||  |||||||||  |||||||||  |||||||  |||||  ||  ||  |||
Db       1164 AGCCTGCTGAGCACTGAAGCCAAGTTGGTCTCAGCCACTGGGGGTCCCCTGCCTCCAGTC

Qy       1141 AGCACCCTGACAGCACTGCACAGCTTGGAGCAGACATCCCCAGGCCTCAACCAGCAGCCC
             ||||||||||||||||||||||  ||||||||||||  ||  |||||  ||||||||||||||
Db       1224 AGCACCCTGACAGCACTGCACAACTTGGAGCAGACGTCTCCAGGTCTCAACCAGCAGCCA

Qy       1201 CAGAACCTCATCATGGCCTCACTTCCTGGGGTCATGACCATCGGGCCTGGTGAGCCTGCC
             ||||||||||||||||  |||||  ||||||||||||||||  ||  |||||  |||||||||
Db       1284 CAGAACCTCATCATGGCTTCACTGCCTGGGGTCATGACCATTGGACCTGGGGAGCCTGCC

Qy       1261 TCCCTGGGTCCTACGTTCACCAACACAGGTGCCTCCACCCTGGTCATCGGCCTGGCCTCC
             ||||||||  ||  ||  |||||  ||||||||  |||||  ||||||||||  ||  |||||||||
Db       1344 TCCCTGGGCCCCACATTCACTAACACAGGCGCCTCTACCCTGGTCATTGGTCTGGCCTCC
Qy       1321 ACGCAGGCACAGAGTGTGCCGGTCATCAACAGCATGGGCAGCAGCCTGACCACCCTGCAG
             ||  ||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db       1404 ACTCAGGCACAGAGTGTGCCGGTCATCAACAGCATGGGCAGCAGCCTGACCACCCTGCAG

Qy       1381 CCCGTCCAGTTCTCCCAGCCGCTGCACCCCTCCTACCAGCAGCCGCTCATGCCACCTGTG
             ||  ||||||||||||||||  ||||||||||||||||||||||  ||||||||  |||||
Db       1464 CCGGTCCAGTTCTCCCAGCCACTGCACCCCTCCTACCAGCAGCCACTCATGCCCCCTGTA

Qy       1441 CAGAGCCATGTGACCCAGAACCCCTTCATGGCCACCATGGCTCAGCTGCAGAGCCCCCAC
             ||||||||  |||  ||||||  ||||||||||||||||||  ||||||||||||||||||
Db       1524 CAGAGCCACGTGGCCCAGAGTCCCTTCATGGCCACCATGGCCCAGCTGCAGAGCCCCCAC

Qy       1501 GCCCTCTACAGCCACAAGCCCGAGGTGGCCCAGTACACCCACACGGGCCTGCTCCCGCAG
             ||||||||||||||||||  ||||||||||||||||  |||||  |||||||  ||||||
Db       1584 GCCCTCTACAGCCACAAGCCTGAGGTGGCCCAGTACACGCACACAAGCCTGCTTCCGCAG

Qy       1561 ACTATGCTCATCACCGACACCACCAACCTGAGCGCCCTGGCCAGCCTCACGCCCACCAAG
             ||||||||  |||||  |||   ||||||||  ||||||||  ||||||||||||||||||||
Db       1644 ACTATGCTGATCACGGAC---ACCAACCTCAGCGCCCTTGCCAGCCTCACGCCCACCAAG

Qy       1621 CAGGTCTTCACCTCAGACACTGAGGCCTCCAGTGAGTCCGGGCTTCACACGCCGGCATCT
             ||||||||||||||||||  ||||||||||||||  |  ||  |||||    ||   |  |||
Db       1701 CAGGTCTTCACCTCAGACACAGAGGCCTCCAGTGAGCCTGGACTTCATGAACCATCGTCT

Qy       1681 CAGGCCACCACCCTCCACATCCCCAGCCAGGACCCTGCCGGCATCCAGCACCTGCAGCCG
             |  |||||||||  ||||||||||||||||||||||  |  ||||||||||||||||||||
Db       1761 CCAGCCACCACCATCCACATCCCCAGCCAGGACCCATCTAGCATCCAGCACCTGCAGCCG

Qy       1741 GCCCACCGGCTCAGCGCCAGCCCCACAGTGTCCTCCAGCAGCCTGGTGCTGTACCAGAGC
             ||  ||||||||||||  ||||  |||||  ||||||||||||||||||||  ||||||||||
Db       1821 GCTCACCGGCTCAGCACCAGTCCCACCGTGTCCTCCAGCAGCCTGGTGTTGTACCAGAGC

Qy       1801 TCAGACTCCAGCAATGGCCAGAGCCACCTGCTGCCATCCAACCACAGCGTCATCGAGACC
             ||  |||||||  |||  ||  ||  ||||||||||||||||||||  |  ||||||||||
Db       1881 TCGGACTCCACCAACGGGCATAGCCACCTGCTGCCATCCAACCATGGTGTCATCGAGACT

Qy       1861 TTCATCTCCACCCAGATGGCCTCTTCCTCCCAGTAA 1896
```

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                  || |||||||||||||||||||| ||||||||||||
Db        1941 TTTATCTCCACCCAGATGGCCTCCTCCTCCCAGTAA 1976
```

Regarding claim 2, the fragment of Emens comprises 22 contiguous nucleotides (see above alignment).

Regarding claims 3 and 4, Emens teaches an allele-specific oligonucleotide hybridizing to the fragment of claim 1, or a complement thereof (see Methods section, page 7000, col. 2, where the above sequence, including the underlined fragment, was used as a specific probe for a complementary sequence).

5. Claims 1-6 are rejected under 35 U.S.C. 102(e) as being anticipated by Wang (US 2004/0181048 A1; filed August 8, 2001).

Regarding claim 1, Wang teaches a nucleic acid fragment comprising more than 10 contiguous nucleotides of SEQ ID No: 3 and the polymorphic nucleotide T at position 29 (see alignment below). This alignment was generated from SEQ ID No: 519026 of Wang.

```
RESULT 4

; Publication No. US20040181048A1
; GENERAL INFORMATION:
;  APPLICANT: Wang, David G.
;  TITLE OF INVENTION: Identification and Mapping of Single
;  TITLE OF INVENTION:  Nucleotide Polymorphisms in the Human Genome
;
; SEQ ID NO 519026
;   LENGTH: 678
;   TYPE: DNA
;   ORGANISM: Homo sapiens


  Query Match             100.0%;  Score 93;  DB 4;  Length 678;
  Best Local Similarity   100.0%;  Pred. No. 2e-18;
  Matches   93;  Conservative    0;  Mismatches    0;  Indels    0;  Gaps
0;
```

```
Qy          1 GTAAGGTCCAGGCCTGCTGGCCCTCCCTTGGCCTGTGACAGAGCCCCTCACCCCCACATC 60
              ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db        359 GTAAGGTCCAGGCCTGCTGGCCCTCCCTTGGCCTGTGACAGAGCCCCTCACCCCCACATC 300

Qy         61 CCCCGGGCTCAGGAGGCTGCTCTGCTCCCCCAG 93
              |||||||||||||||||||||||||||||||
Db        299 CCCCGGGCTCAGGAGGCTGCTCTGCTCCCCCAG 267
```

Regarding claim 2, the fragment of Wang is 93 nucleotides in length (see above).

Regarding claims 3 and 4, Wang teaches an allele-specific oligonucleotide probe hybridizing to a complement of the nucleic acid fragment of claim 1 (the above fragment hybridizes specifically to an oligonucleotide fragment complementary thereto; see also paragraphs 10 and 20-21, where Wang teaches that the fragments may be used as probes).

Regarding claims 5 and 6, Wang teaches that the above fragment may function as a primer with the 3'end arranged at the polymorphic site of the fragment (see paragraph 21).

Response to Arguments

6. Objections to the Specification

Applicant's arguments, see page 4, filed October 18, 2006, with respect to the corrections to the specification have been fully considered and are persuasive. The submission of a Sequence Listing and identification of the sequences shown in the Figures overcomes the objection, and therefore, it has been withdrawn.

Rejections under 35 U.S.C. 102

A. Emens

Applicant's arguments (page 4) filed October 18, 2006 have been fully considered but they are not persuasive.

In response to applicant's argument that the references fail to show certain features of applicant's invention, it is noted that the features upon which applicant relies (i.e., the instant HNF1 nucleic acid fragment is expressed in a human cell line rather than the Hamster insulinoma cell line taught by Emens) are not recited in the rejected claim(s). Although the claims are interpreted in light of the specification, limitations from the specification are not read into the claims. See *In re Van Geuns*, 988 F.2d 1181, 26 USPQ2d 1057 (Fed. Cir. 1993).

Applicant also argues that Emens does not teach that the HNF1a nucleic acid fragment is associated with MODY in humans (page 4). In response to applicant's arguments, the recitation "for the diagnosis of maturity onset diabetes of the young (MODY) or the risk of MODY in humans" has not been given patentable weight because the recitation occurs in the preamble. A preamble is generally not accorded any patentable weight where it merely recites the purpose of a process or the intended use of a structure, and where the body of the claim does not depend on the preamble for completeness but, instead, the process steps or structural limitations are able to stand alone. See *In re Hirao*, 535 F.2d 67, 190 USPQ 15 (CCPA 1976) and *Kropa v. Robie*, 187 F.2d 150, 152, 88 USPQ 478, 481 (CCPA 1951).

Therefore, since Emens teaches the specific structural features recited in the instant claims 1-4, the rejection is maintained.

B. Wang

Applicant's arguments filed October 18, 2006 have been fully considered but they are not persuasive. Applicant presents two arguments discussed below.

Applicant's first argument is that Wang does not anticipate the instant claims, because Wang teaches the reverse complement of the instant SEQ ID NO: 3 rather than SEQ ID NO: 3. This argument was not found persuasive, because Wang's teaching of the sequence complementary to SEQ ID NO: 3 is an inherent teaching of the instant SEQ ID NO: 3. In other words, by disclosing a sequence with more than 10 nucleotides complementary to SEQ ID NO: 3 and further including the claimed substitution at position 29, Wang implicitly discloses the complementary sequence (more than 10 nucleotides of the instant SEQ ID NO: 3 with the claimed substitution).

Regarding the implicit teachings of Wang, MPEP 2123 notes, "The use of patents as references is not limited to what the patentees describe as their own inventions or to the problems with which they are concerned. They are part of the literature of the art, relevant for all they contain." *In re Heck*, 699 F.2d 1331, 1332-33, 216 USPQ 1038, 1039 (Fed. Cir. 1983) (quoting *In re Lemelson*, 397 F.2d 1006, 1009, 158 USPQ 275, 277 (CCPA 1968)). A reference may be relied upon for all that it would have reasonably suggested to one having ordinary skill the art, including nonpreferred embodiments. *Merck & Co. v. Biocraft Laboratories*, 874 F.2d 804, 10 USPQ2d 1843 (Fed. Cir.), *cert. denied,* 493 U.S. 975 (1989). See also *Celeritas Technologies Ltd. v. Rockwell International Corp.*, 150 F.3d 1354, 1361, 47 USPQ2d 1516, 1522-23 (Fed. Cir. 1998) (The court held that the prior art anticipated the claims even though it taught away from the claimed invention. "The fact that a modem with a single carrier data signal is shown to be less than optimal does not vitiate the fact that it is disclosed.")." Since the disclosure by Wang of a sequence complementary to the instant SEQ ID NO: 3 would have reasonably suggested the

complementary sequence to one having ordinary skill in the art, Wang anticipates the instant claims 1-6.

Furthermore, claim 1 recites that the nucleic acid fragment contains 10 or more contiguous nucleotides and also the relevant polymorphism derived from SEQ ID NO: 1, SEQ ID NO: 3 or a complement thereof. Therefore, Wang's teaching of a sequence comprising the C->T polymorphism and 10 contiguous nucleotides complementary to SEQ ID NO: 3 anticipates claim 1.

Applicant's second argument is that Wang does not teach association of the HNF1a nucleic acid fragment with MODY in humans (page 5). In response to this argument, the recitation "for the diagnosis of maturity onset diabetes of the young (MODY) or the risk of MODY in humans" has not been given patentable weight because the recitation occurs in the preamble. A preamble is generally not accorded any patentable weight where it merely recites the purpose of a process or the intended use of a structure, and where the body of the claim does not depend on the preamble for completeness but, instead, the process steps or structural limitations are able to stand alone. See *In re Hirao*, 535 F.2d 67, 190 USPQ 15 (CCPA 1976) and *Kropa v. Robie*, 187 F.2d 150, 152, 88 USPQ 478, 481 (CCPA 1951).

Therefore, since Wang teaches the specific structural features recited in the instant claims 1-6, the rejection is maintained.

Conclusion

No claims are currently allowable.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL.** See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Angela Bertagna whose telephone number is 571-272-8291. The examiner can normally be reached on M-F, 7:30 - 5.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Benzion can be reached on 571-272-0782. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Angela Bertagna
Examiner, Art Unit 1637
November 17, 2006

amb

JEFFREY FREDMAN
PRIMARY EXAMINER
11/22/06